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THE CRISIS IN HUMAN PARTICIPANTS RESEARCH: IDENTIFYING THE PROBLEMS AND PROPOSING SOLUTIONS

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Today, almost no one is happy with the process of protecting human participants in clinical research. Clinical investigators are frustrated with the review process, which seems bureaucratic and inefficient, burdening them with minor details rather than helping them ensure participants' safety. IRB members feel overworked, baffled by ambiguous regulations, fearful of federal audits, and anxious about calls for accreditation of uncertain benefit. Federal regulators are aggravated by the limited scope of their authority and variable adherence to regulations, and worried about criticism from Congress and the public for inaction in the face of mounting harms to research participants. Commercial sponsors of clinical research see the system as time consuming, repetitive, and inefficient, with delays costing millions of dollars. Foreign researchers and governments often view the imposition of U.S. regulations as culturally insensitive and even imperialistic. The public finds each death during a research study and each new case of allegedly unethical practices worrisome and indicative that the system is broken.

Many are attempting to respond to these problems. In 2000, the Department of Health and Human Services (DHHS) disbanded the Office for Protection from Research Risks (OPRR) and created the Office for Human Research Protections (OHRP). OHRP has simplified the assurance process through the Federalwide Assurance system. Similarly, the Food and Drug Administration (FDA) recently created the Office of Good Clinical Practice to maintain high ethical standards in clinical trials. The National Institutes of Health (NIH) has issued new requirements for the training of researchers on human participants protection and has offered one-time grants to improve IRB performance. The Veterans Administration has established an accreditation program developed by the National Commission for Quality Assurance for its facilities. Association for the Accreditation of Human Research Protection Programs (AAHRPP) has recently begun accrediting IRBs. DHHS commissioned the Institute of Medicine (IOM) to examine IRBs and make recommendations about how to improve them, including evaluating the merits of these accreditation programs. Finally, Congress has determined that the situation is sufficiently serious to merit special hearings; at least two bills have been proposed on these issues.

It is not an exaggeration to say that there is an impending, if not actual, crisis in the oversight of human participants research. Current responses are significant; they evidence the mobilization of enough attention to engender meaningful reform. However, they are also problematic. They mainly address specific problems that have attracted the public attention, such as researcher's conflict of interest or IRBs' heavy workloads, and utilize the existing system mandated in the federal regulations. This crisis would be better served by a comprehensive re-visioning of how to ensure an ethical and safe clinical research system. Such a goal can only be achieved by carefully examining the problems permeating the current system and developing a comprehensive response tailored to resolving most of them.

THE PROBLEMS

A series of major scandals in the late 1960's and early 1970's, culminating in revelations about the Tuskegee syphilis study, generated sufficient public pressure to create a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974. The Commission recommended a regulatory system focused on local IRB review and individual informed consent. Its proposal was largely implemented in the federal regulations governing human participants research known as the "Common Rule" (45 CFR 46). This system has prevented controversies on the scale of Tuskegee, but over the last two decades, its weaknesses have become more manifest. Fifteen specific problems, many of which have been previously identified by the Office of the Inspector General (OIG) and the National Bioethics Advisory Commission (NBAC), afflict the current system of research review and oversight. They can usefully be grouped into three broad categories: 1) Problems with the structure of the review and oversight system; 2) Problems with the IRB review process, and 3) Problems with the assessment of the review and oversight system and IRB process.

Before delineating the problems with the current human research participants protection system it should be noted that for many of these problems there simply is no data. Consequently, we have relied on various sources: 1) our own personal experience as researchers and IRB members; 2) discussions with researchers, IRB members and staff, pharmaceutical company representatives, regulators, and others, 3) findings from OHRP actions against institutions, and 4) the few available reports, such as those from the Office of the Inspector General, the National Bioethics Advisory Commission, and the General Accounting Office. We recognize these are anecdotes and fall far short of data, but they are the best evidence available. Indeed, in our view, the lack of systematic data-or even a process for collecting systematic data-about clinical research performance and the human research participants protection system is itself a major problem, and is a reason to consider seriously comprehensive reform.

TABLE 1: Problems with the Current Human Research Protection System

PROBLEMS	DESCRIPTIONS OF PROBLEMS
I) PROBLEMS IN THE STRUCTURE OF THE HUMAN RESOURCE PARTICIPANTS PROTECTION SYSTEM	
1. Not all research covered by federal regulations	Regulations only apply to research funded by the federal government or seeking FDA approval of drugs, biologies, or devices. Most major research institutions apply the regulations to all research, including non-federally funded research.
2. No mechanism for addressing major ethical issues	The federal regulations state that "The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility." IRBs have few resources and little clout to consider more general ethical issues. National attention to ethical issues in research is sporadic.
3. Exclusive reliance on local, institution-based review	Local IRB review is not inherently ethical or unethical. Not well suited to the increasing volume of non-institutional based research, creates uneven distribution of work among IRBs, uneven scrutiny, dissipates time and resources, and allows "IRB shopping."
4. Absence of resources devoted to IRBs	Most IRB members are not compensated or recognized for their efforts. This is demoralizing and also makes it difficult to recruit and retain members. Lack of resources compromises administrative support for IRB, development of infrastructure and policies.
5. Lack of attention to inherent institutional conflicts of interest	Little attention is paid to the fact that IRBs review the research conducted by the institution they are under the auspices of.
6. Poorly defined IRB role in identifying and managing researchers' and IRB members' conflicts of interest	Current system regarding investigators' and IRB members' individual conflicts of interest is complex. IRB role is poorly defined for these and other individual conflicts. Some are handled poorly; others are not detected.
7. Inadequate education of clinical investigators and IRB members	Educational requirements on human participants research exist only for federally funded researchers and IRBs. These requirements and curricular content are ill-defined and inadequate.
8. Repetitive Review process	Research studies conducted at multiple sites must be reviewed by each site's IRB. This process dissipates resources, adds to time of review process, and frustrates investigators.
II) REVIEW PROCESS	
9. Time-Consuming review process	Slow process of review demoralizes investigators and can hinder access to last chance experimental therapies. Many factors slow the review process: review by other committees, low frequency of IRB meetings, need for revisions and re-review, low quality of submitted research studies, and slow rate of returning revised research studies.
10. Poor quality control of IRB reviews	IRBs must often review research studies they lack expertise in and fail to reference outside sources or consult experts in order to understand a research study. Limited ability to audit data offered to them for continuing review.
11. Excessive focus on informed consent forms	IRBs often focus on minor changes in informed consent forms at the expense of other important ethical issues.
12. Deficiencies in monitoring and continuing review	IRBs do not undertake monitoring or continuing review with appropriate seriousness; they are often too busy to spend sufficient time on it.
13. Inefficient and ineffective adverse event reporting	Process of adverse event reporting is vague. When adverse events are reported, analyzing the data is unnecessarily difficult and repetitive.
III) PROBLEMS IN PERFORMANCE ASSESSMENT	

14. Insufficient evaluation of IRB effectiveness	IRBs are not systematically evaluated, so the quality of their work cannot be ensured and unjustified variability corrected.
15. No systematic collection and dissemination of performance data	No comprehensive data exist on human participants in clinical research, or on specific aspects of that research.

I) Problems in the Structure of the Human Research Participants Protections System

1. Not all health research[1] is covered by the federal protections. To receive either federal research funding or FDA approval for drugs, biologics, or devices, research institutions must abide by the federal regulations for human participants research. The regulations, however, do not apply to privately funded research not seeking FDA approval. Institutions receiving funding from the DHHS must also negotiate an assurance with OHRP, formalizing its commitment to adhere to the federal regulations and to protecting human participants. The vast majority of major research institutions voluntarily undertake to extend this agreement to non-DHHS funded research. But most research is no longer conducted at such institutions.

Ironically, the types of research outside the federal regulations are often both socially and ethically controversial. For example, reproductive research, research on new surgical procedures, and "quality research," on how to improve institutions, constitute much unregulated research. The remaining safeguards - publication and peer review - cannot ensure the ethical permissibility of research, nor can they prevent unethical research practices before they are perpetrated.

Many other negative outcomes stem from the short reach of the federal protections. First, a protocol's source of funding determines the oversight process, rather than the more relevant question of its risks to human participants. Second, participants should not have to know who funds the research study in order to be assured of adequate protection. Third, society benefits from research; its members should feel certain that abuses do not occur for their benefit. Fourth, the public assumes that human participants research is under one regulatory system. Finally, many ethically problematic practices might have been subject to extensive prospective public debate or avoided had there been oversight of private research.

2. No Mechanism for Addressing Major Ethical Issues. Clinical research can involve a wide variety of highly controversial issues, ranging from the inclusion of illiterate participants in developing countries to payment to children for participation in research, from xenotransplantation to the cloning of embryos, from conceiving a child in order to cure a sibling to the provision of an intervention after the research is completed. These issues can become major social controversies themselves engendering different assessments within and across IRBs.

According to the federal regulations, in evaluating research protocols, IRBs are supposed to concentrate on risk-benefit ratios, subject selection, and informed consent. The federal regulations state that "The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility"(45CFR46.111(a)(2)). Importantly, given the local nature of IRB review, even if a single IRB did make assessments on these larger ethical issues, it would lack any clout in applying or disseminating its assessment. Sponsors and investigators can ignore the impact of a single local IRB's decision by shifting research to other institutions.

In addition, when IRBs do consider some of the issues, such as payment to children in the context of a specific research project, they typically have not been able to devote the time and resources to thoroughly reflect and discuss the issue. The result can be the formation of ad hoc and premature policies or no policies at all, often with little public education or discussion. Indeed, IRBs may even overlook an issue altogether because they are unaware of its ethical significance.

There have been some efforts to address these larger ethical issues, including the National Bioethics Advisory Commission, the President's Council on Bioethics, the Institute of Medicine, and other bodies. However, these efforts have been sporadic and unsystematic, usually focused on the latest controversy. More importantly, they have lacked a mechanism to effect their decisions in terms of policies.

3. Exclusive reliance on local, institution-based review. Because during the nascent years of research review, most human participants research occurred at a few major centers and because of the American bias against central authority, the U.S. system for review of human research participants is grounded in local, institution-based review. However, this structure is not intrinsically valuable. Many other countries have adopted effective regional or national research ethics review boards. Of course, the current system is not intrinsically unethical either, but it does cause serious problems.

First, the local, institutional based structure of IRB review increasingly seems anachronistic in an era when industry funds a majority of clinical research and a substantial proportion-maybe even most-of clinical research is no longer conducted at academic medical centers, but through private physicians' offices, clinics, and contract research organizations (CROs). Second, it promotes repetitive review of multi-site research studies, which is discussed later in the paper. Third, it creates an uneven distribution of work among IRBs. IRBs at large, busy institutions can have a high volume of protocols to review, overwhelming even the most competent IRB, while IRBs at smaller institutions often review fewer studies. While not yet documented by rigorous studies, having very few protocols to review could limit members' familiarity with important issues and impede the development of standard operating procedures and policies. Fourth, sustaining the estimated 4 to 6,000 IRBs when fewer would suffice if the workload were more evenly distributed dissipates precious resources and expertise. Finally, it allows "IRB shopping," the strategic selection of an IRB likely to grant favorable review especially for pharmaceutical or device research not being conducted at academic institutions.

4. Absence of resources devoted to IRBs. At most institutions, IRBs have been underfunded and under staffed. They do not receive specific support from the NIH or other bodies so funding must be taken from general administrative costs and compete with many other pressing priorities. In addition, IRB members work under remarkably demanding conditions; as a group, they are continuously inundated with protocols, undertake complex analyses of a wide range of topics, and juggle IRB membership with numerous other responsibilities. Though independent IRBs usually nominally compensate members for their efforts, academic research institutions typically pay only lay members and IRB chairs, and sometimes not even them. Also, IRB members' dedication is rarely publicized to their peers, and when publicized may not be viewed as a positive communal contribution, making IRB membership as unrewarding collegially as it is monetarily.

This lack of compensation or recognition communicates to IRB members a devaluation of their commitment to ethical research. This is demoralizing, but its secondary repercussions are damaging on a practical level: there is anecdotal evidence that many IRB chairs are having difficulty securing and retaining qualified IRB members. Perhaps the current system attracts some people truly committed to IRB review on firm ethical grounds. However, additional qualified individuals, who may require other incentives, are much needed as well.

In addition, the lack of resources compromises administrative and staff support for IRBs which are invariably undervalued. Minutes at IRB meetings make take months to write up; comments back to researchers can be delayed; proper documentation may not occur. In addition, the lack of resources precludes the development of essential but expensive infrastructure such as computerized protocol systems or adverse event reporting systems.

5. Lack of attention to inherent institutional conflicts of interest. As a consequence of the Gelsinger case and controversies at some major academic research institutions, researchers' conflicts of interest have attracted substantial concern and attention. However, much less examined are the IRB conflicts of interest inherent in the current system. Through IRB oversight and review, institutions demonstrate their commitment to ethically sound research. However, the IRB is under the auspices of the very institution conducting the research they review. And typically, most of the IRB members are employees of the institution. While most IRBs and IRB members are fiercely independent and treasure their integrity, this is a potential conflict of interest. It makes the IRB and individual members susceptible to the influence of powerful officials and researchers within the institution. Indeed, IRB members could feel inclined to tolerate otherwise unacceptable practices that are either perceived as difficult to change at their home institution or have large financial implications.

6. Poorly defined IRB role in identifying and managing investigators' conflicts of interest. The current system regarding investigators' financial conflicts of interest is complex and ill-defined. Researchers might have to comply with as many as four different conflict of interest requirements; those from the NIH, the FDA, separate institutional policies and even policies of their professional societies. Since not all of these requirements are consistent, it is unclear which takes precedence. In addition, the IRBs responsibilities for ensuring investigators' compliance with conflict of interest requirements are unclear at best. As a consequence, some conflicts may be disclosed and unnoticed, and others managed in variable and sometimes conflicting ways.

7. Inadequate education of clinical investigators, IRB members, and IRB staff. Standardized, federal educational requirements for handling animals in basic research were instituted in 1985. Yet even now, neither clinical researchers nor IRB members nor IRB staff are systematically educated on the ethics of human participants research. In fact, only those receiving federal funds must adhere to one of several educational requirements, all from the NIH. All applicants for NIH institutional training grants must describe their past or upcoming training in the responsible conduct of research. However, no curricular requirements are specified; there is no assurance that important ethical issues are included in the training. Most importantly, this requirement has limited applicability to those who receive the training grants, excluding senior scientists and many junior scientists. Second, in 2000, the NIH adopted a more comprehensive requirement that all investigators submitting NIH grant applications must provide evidence of training in human participants protections for themselves and key research personnel. This requirement lacks specific curricular criteria. The main guidance comes from reference to three NIH focused computer-based courses. One is a 1 hour course required of all researchers and key personnel in the NIH Intramural Research Program; another provides specific information about IRB members' roles and responsibilities that is required for all intramural NIH IRB members. The newest course is designed for anyone involved in human participants research, including extramurally funded researchers. Though helpful, computer-based training may be particularly vulnerable to being a half-hearted activity.

While some education requirements are better than none, they apply only to recipients of NIH funds, lack curricular specifications, and fail to allocate resources to develop essential educational materials or programs. The NIH awards grants for the development of short courses on ethical issues in research and K-awards for training health professionals in research ethics, particularly human participants research.

8. Repetitive review process. Adding to the lengthy review period for some research studies is the fact that many studies require review by scores or even hundreds of IRBs. Research studies conducted at multiple sites must pass through review at each site. Even when conducted at one site, research involving multiple investigators must be reviewed at each investigator's home institution.

This multi-layered review process can take more than a year to complete. If one IRB stipulates changes to a protocol, those changes may also need to gain the approval of the other IRBs. Additionally, when a single protocol is under concurrent review at many different IRBs, those IRBs may release differing or even contradictory judgments on specific issues, such as participant eligibility criteria or the content of an informed consent document. Further, just keeping track of IRB review and modifications can become a full time job, without any added value. All this effort perpetuates some investigators' feelings that they must endure IRB review, rather than participate in or learn from it.

II) Problems in the IRB Review Process

9. Time-consuming review process. Investigators commonly complain about the slow pace of IRB review, even for low risk studies. "Scientific review," which typically precedes IRB review, can account for part of this

delay. It is frequently conducted by a separate panel, which focuses exclusively on the study's scientific validity, merit, and methodology. Even at very busy institutions, these panels typically meet once a month; thus, pending revisions, scientific review can consume months prior to the initiation of IRB review. In some cases, IRBs also review the science of a research study after the completion of scientific review, further extending the review process.

Other factors also contribute to the sluggish rate of review. Some research studies are subject to review by other safety committees, like the radiation safety committee, which further extend the review process. Second, many IRBs even at major institutions meet infrequently, commonly only once a month; if a research study misses review at one meeting, it is not considered again for some weeks. Finally, IRBs usually return a research study to investigators with several stipulations for revisions. Once the investigators have revised the research study, either the chair or the entire committee must review it again. (OHRP is discouraging review by the chair alone and encouraging full committee review of investigator responses to stipulations, further prolonging the review process.)

Investigators can become frustrated by the length of time required for the review process, contributing to the sentiment that IRB review is bureaucratically driven and of little benefit. This attitude only decreases investigators' appreciation for the intrinsic value of ethical research. Investigators, though, can also hinder the review process. There is no standard in place to ensure the high quality of submitted research studies and few IRBs have the resources to develop templates and pro-active guidance. A poorly composed research study takes additional time for IRBs to decipher and may require more revisions. In addition, investigators sometimes take weeks or months to return revised research studies to the IRB.

10. Variable quality and expertise of IRB reviews. A single IRB often reviews research on a wide variety of scientific topics and research settings, some of which are not aligned with the scientific expertise of the board members. For instance, IRBs may need to review research studies using drugs or interventions that lie outside the expertise of any of the members. Similarly, IRBs may review research studies being conducted in a developing country when none of the IRB members have first hand experience much less professional expertise concerning the health care infrastructure or social and cultural practices of that country. Further, vital information about experimental drugs or interventions may not be published but only known by experts in the research area through conference presentations or word of mouth. To remedy these deficiencies in information, IRBs can consult experts or investigate external materials some of which may not even be published. This requires a commitment of IRBs limited resources and time, and therefore may not be readily done. Indeed, it is fair to say that IRBs are relatively passive, responding to the information provided rather than actively seeking information in addition to that submitted in the research protocol. Under these circumstances, IRBs can make poor decisions about the permissibility of a study that can sometimes result in avoidable harms to participants.

11. Excessive focus on informed consent forms. Many espouse the view that informed consent is the fundamental basis of ethical human participants research. The only access IRBs have to the informed consent process is through the informed consent forms. Further, many regulatory and enforcement actions-and increasingly law suits-focus on what details were included in the informed consent documents, especially whether specific harms that resulted were listed. These factors conspire to produce a disproportionate emphasis by IRBs on the content and wording of informed consent documents, sometimes derisively called "wordsmithing." While informed consent is vital, it is not sufficient to make research ethical. Indeed, informed consent does not seem to be the problem that generated the major controversies in research ethics within the last few years. For example, the ethical problems surrounding the recent death of Jesse Gelsinger during a gene therapy trial at the University of Pennsylvania would not have been rectified by a better informed consent form. The death of a healthy research subject at the University of Rochester would not have been rectified by a more complete listing of risks. Present day worry over informed consent forms usurps attention from more protean but deeper philosophical, social, and cultural questions raised by research with human participants.

12. Deficiency in monitoring and continuing review. Monitoring and continuing review allows IRBs to account for the ethical permissibility of a research study over the course of its progression, in order to tailor the protections to the actual experience in the study. IRBs both track changes to the study, such as alterations to the informed consent form, as well as review each study on an regular or at least annual basis whether it is altered or not. For monitoring and continuing review, IRBs have access to information like a summary of changes to the protocol, data on participant enrollment, data on unanticipated problems, a review of relevant literature, and plans to change the protocol.

Despite the important purpose of monitoring and continuing review, federal regulations do not specify the process an IRB must undertake to properly fulfill them. As a result, in 1981, the President's Commission found that "many IRBs do not understand what is expected in the way of 'continuing review.'" Not much has changed over time. The Office of the Inspector General and others have found that with respect to continuing review, IRB conduct was "hurried and superficial." Thus a combination of lack of specific guidance and time pressures have made continuing review perfunctory at best. Yet, many of the problems uncovered with current research practices arise after continuing review and seem that they might have been avoided with more thorough and careful monitoring and continuing review.

13. Insufficient and inefficient adverse event reporting system. A key to protecting research participants is monitoring the actual safety of on-going research trials. And central to this process, are adverse event reports. Such reports help in determining how risky the research actually is and how these risks might be minimized. In the current system, IRBs receive adverse event reports from investigators, sponsors, FDA officials, and DSMBs. This task is made unnecessarily difficult by the variable and inefficient nature of adverse event reporting.

The FDA regulations for adverse event reporting related to new drugs and devices seeking regulatory approval are precise, outlining different types of adverse events and timelines for reporting them. (21 CFR 312.32(a); 21 CFR 812.2(s)). By contrast, the federal regulations-the "Common Rule"-that apply to adverse event reporting for all other types of research, including with existing drugs and devices, are vague. They require only that IRBs ensure that the protocol "makes adequate provision for monitoring the data collected to ensure the safety of subjects" (45CFR46.111(a)(6); 21 CFR 56.111(a)(6)). Nor do the regulations specify what counts as an adverse event or to whom they should be reported. Some institutions, such as the NCI, have spent millions of dollars creating a comprehensive and uniform adverse event scale and reporting system. But this is not uniform

throughout the system. As a result, adverse events reports reach IRBs in different ways and at different times, without any procedural uniformity or substantive standardization. This variability can make extracting useful information from adverse event reports challenging.

However, even more problematic is the manner in which the data is delivered to the IRB. Each event is reported independently, separated from meaningful background data. A local IRB cannot determine whether the type of event is prevalent or usual, or if the event was caused by the research intervention or a mitigating factor, like a reaction to standard treatment. Large, multi-sites studies usually have a higher number of adverse events, each reported to many different IRBs. Then each of the local IRBs is entrusted with the identical task of determining whether the event is serious and what should be done.

In addition, the relationship between IRBs and other bodies entrusted with reviewing adverse events, such as DSMBs, is unclear. Consequently, data available to the DSMB usually may not be provided to the IRB overseeing the research study. While adverse event reporting may be the most important mechanism to monitor and minimize the risks of research, the current system is both inefficient and ineffective. We lack a uniform systematic, real time adverse event reporting system that could really protect patients from unnecessary risks.

III) Problems in Performance Assessment

14. Insufficient evaluation of IRB effectiveness. At its most basic, the purpose of IRB review is to protect human research participants. Yet no one can say how effective IRBs actually are at achieving this basic mission. There have been no systematic reviews of IRB function, there is no on-going systematic monitoring of IRB functioning, and the number of IRB aberrations that are brought to the attention of the OHRP or FDA each year serve only as a crude tool for measuring the conduct of either an individual IRB or the whole human research participant protections system. As a result, many important issues are unresolved, including a definition of the optimal composition of an IRB, the optimal number of research studies for an IRB to review each year, and the appropriate number of administrative and support staff for an IRB. In addition, the absence of performance data preclude examining variability between IRBs and narrowing inappropriate variability in performance. Without obtaining such data and exploring questions such as these, a high quality human research participant protection system cannot be ensured.

15. No systematic collection and dissemination of performance data. Amazingly, no one-not the director of NIH, the commissioner of the FDA, or a representative of the Pharmaceutical Researcher and Manufacturers of America-knows how many people participate in biomedical or other research studies in the United States each year. No one knows how many people are in different types of studies; how many participate in studies at academic institutions, in private practices, through contract research organizations, or health maintenance organizations; or how many participate in studies funded by the federal government, pharmaceutical and biotechnology companies, or charitable foundations. Nor does anyone know how many studies sponsored by public or private US funds are conducted in foreign countries, or the number of participants in these studies.

Similarly, no comprehensive data exist on specific aspects of research. No one can say how many research participants suffer serious, unexpected adverse events each year, either for a specific study or in general, and of those, how many sustain a permanent disability or die unexpectedly. Nor can anyone say how many people are paid to participate in research, how many receive therapy for their disease, or how these numbers vary by race, gender, age, socioeconomic status, or other factors.

The FDA does collect some data on research projects under its jurisdiction. Yet most of these data are not electronic, not systematized, and some are not publicly released. Instead, they are used as a more general audit mechanism.

It seems difficult to know much about the actual safety and protection of human research participants without such basic data. There is no mechanism in place to collect such data in real time.

PROPOSED REFORMS

These problems surrounding the protection of human participants in clinical research have not gone unnoticed. As noted, the OIG and NBAC as well as many researchers and bioethicists have identified many of these problems. Others have begun efforts to address some of them. We mentioned recent NIH initiated reforms in investigator and IRB member education. Other efforts include accreditation, credentialing of IRB professionals, legislative action, quality improvement programs, and the creation of a central IRB. Though these efforts may make significant strides in some areas, they respond mainly to concerns about the limits of federal oversight and the quantity of protocols facing IRBs. At best, these efforts are partial solutions. Most importantly, all the current proposals fail to address the fundamental structural problems afflicting the system of research review that are derived from the nature of the federal regulations and the lack of funding for IRBs.

TABLE 2: How Well the Proposed Reforms Address the Problems with the Human Research Participants Protection System

PROBLEMS	ACCREDITATION	CREDENTIALING IRB PROFESSIONALS	LEGISLATIVE PROPOSALS	OHRP QUALITY IN MANAGEMENT PROGRAMS	CENTRAL IRBS

1. Not all research covered by federal regulations	No	No	Yes	No	No
2. No mechanism for addressing major ethical issues	No	No	No	No	No
3. Exclusive reliance on local, institution-based review	No	No	Partially	No	Partially
4. Absence of resources devoted to IRBs	Partially	No	Partially	Partially	No
5. Lack of attention to inherent institutional conflicts of interest	Partially	No	Partially	No	Partially
6. Poorly defined IRB role in identifying and managing researchers' and IRB members' conflicts of interest	Partially	No	Partially	Partially	No
7. Inadequate education of clinical investigators and IRB members	Partially	Partially	Yes	Partially	No
8. Repetitive review process	No	No	Partially	No	Partially
9. Time-consuming review process	No	No	Partially	No	Partially
10. Poor quality control of IRB reviews	Yes	No	No	Yes	Partially
11. Excessive focus on informed consent forms	No	No	No	No	No
12. Deficiencies in monitoring and continuing review	No	No	No	Partially	No
13. Inefficient and ineffective adverse event reporting	No	No	No	No	Partially
14. Insufficient evaluation of IRB effectiveness	Partially	No	Partially	Partially	No
15. No systematic collection and	No	No	Partially	No	No

dissemination of performance data					

Accreditation. Accreditation of a public or private institution signifies that the institution's human participants protections fulfill certain predetermined standards. Currently, there are two major accreditation initiatives. The department of Veteran Affairs requires all Veterans Affairs Medical Centers (VAMCs) to become accredited by the National Committee for Quality Assurance (NCQA). NCQA requires that institutions file an assurance, which signifies a commitment to both federal and to VA educational requirements. The VA requirements specify that IRB members' qualifications are evaluated prior to their joining an IRB. Institutions must also have written policies and procedures on the identification and management of conflicts of interest, though not on inherent institutional conflicts of interest. Finally, NCQA mandates the evaluation of IRB effectiveness by VAMCs and the IRBs themselves. The NCQA is developing accreditation standards for non-VA IRBs that should be released late in 2002. The second initiative is by AAHRPP that offers all research institutions a voluntary accreditation process. To gain accreditation, IRBs must design written policies and procedures on identifying and managing conflicts of interest. These plans could mediate relationships between IRB members and their home institutions, thereby mitigating inherent institutional conflicts of interest. AAHRPP also has three general requirements. First anyone conducting, supporting, or reviewing human subjects research must demonstrate "sufficient knowledge of the protection of research participants." Second, institutions must give IRBs "adequate resources." Finally, IRBs must have enough time to conduct reviews at a reasonable pace.

At the request of the Department of Health and Human Services, the Institute of Medicine assessed these accreditation initiatives. Its support is at best tepid with several major criticisms. First, the IOM argued "neither [the NCQA nor the AAHRPP's] set of proposed standards applies readily to the full range of research involving human participants or the diversity of research institutions that conduct it." It did endorse the NCQA standards as more promising contending that the AAHRPP's standards lacked specificity and focused too much on documentation. Overall, the IOM argued that because "the proposed standards are new and untested...these emerging accreditation programs are best viewed as pilot projects that will have to be evaluated in light of experience" which, the IOM mused, will take a long time.

Others have argued that accreditation standards must meet three criteria to be effective: they must be 1) required; 2) achievable; 3) measurable or auditable. If a proposed standard does not fulfill these criteria it is not a standard. It is argued that most of the proposed standards fail to meet these criteria and are not effective accreditation standards. While they may be laudatory goals they are not standards of evaluation.

Even if current accreditation standards are deficient, developing optimal standards could solve some of the problems identified. Regarding the structural problems, accreditation could lead to improved education and training for IRB members, investigators, and key personnel. It could also generate pressure that would ultimately enhance resources devoted by institutions to their IRBs. And accreditation might help in improving the management of research conflicts of interest, by requiring written policies and procedures. Accreditation's biggest impact is likely to be related to IRB review processes. Accreditation is likely to facilitate the development of standard operating procedures that encourage a broader focus on elements of research beyond informed consent and ensure IRBs obtain expertise appropriate to the research projects they review. Finally, accreditation may enhance continuing review procedures.

Accreditation has important limitations. First, accreditation cannot solve the structural or performance assessment problems that require changes in the regulations and collaboration and coordination among IRBs. Accreditation will not lead to coverage of all research by federal regulations, elimination of repetitive reviews, streamlining of the review process, or systematic collection of performance data. Second, accreditation is costly in terms of money and time. In the resource poor IRB system, resources devoted to accreditation, both in terms of payment for the review and time devoted by staff toward preparing for the review, are likely to be diverted from other activities. Furthermore, IRBs will inevitably focus their energies fulfilling the accreditation standards. If the standards or feedback are inappropriate, then protections might actually be further compromised. Furthermore, since accreditation is likely to remain voluntary outside the VA system, its impact depends upon the perception by institutional officials that the standards are meaningful and the resources expended in the process worthwhile.

Credentialing IRB Personnel: Having better trained more professional IRB personnel, helping in the research review process could address several problems. Well-trained personnel could streamline the IRB review process. They might also ensure better continuing review, enhance education of IRB members and researchers, and performance assessment of the IRB. However, even the best outcome, credentialing IRB professionals addresses only a small number of the problems facing the human subjects protections system and leaves most of the structural, process or performance problems unchanged.

Legislative Actions: Theoretically, changes in laws and their attendant regulations could create change at both the structural and the local level of the IRB, solving all the problems with the current system. The two leading proposals before Congress-Sen. Kennedy's Research Revitalization Act and the Human Research Subjects Protections Act of 2002 sponsored by Representatives DeGette and Greenwood-have five major provisions in common that address important problems. These proposals require that 1) all human subjects research be subjected to federal regulations; 2) researchers receive education and training; 3) researchers' financial conflicts of interest be disclosed; 4) multi-site research studies receive central IRB review; and 5) basic performance data be collected. Each bill has additional unique provisions. Beginning 6 years after approval, Sen. Kennedy's bill would also require that only an accredited IRB approve all human participants research. The bill would also exempt minimal risk research, such as social science surveys, from IRB review. The DeGette-Greenwood bill mandates the composition of IRBs, requiring that at least twenty percent of the members be "unaffiliated" with the institution. It also defines a new category of "high risk clinical trials," such as those with participants of limited decision-making capacity, for which it requires enhanced safeguards.

These proposals represent major change in human subjects protections. However, as currently drafted, major problems would remain despite the bills. They do not specify where resources for IRBs should come from; they continue to emphasize local IRBs; they do not address the mismatch of IRB expertise and protocol subject matter, or the ineffective adverse event reporting system. As Congress considers these bills their specific provisions are likely to change, and they could address some of the outstanding problems.

OHRP Conflict of Interest and Quality Initiatives: As the federal regulator, OHRP wields considerable authority over many areas of research review and oversight. Institutions conducting research funded by DHHS must file a legally binding

assurance with OHRP attesting to adherence to the federal regulations. OHRP can audit research studies operating under an assurance, and shut down their operation when they are found to be non-compliant. In recent years, OHRP has halted research endeavors at numerous institutions, including Johns Hopkins University and Duke University.

OHRP has initiated a voluntary quality improvement program (QIPs), and issued guidelines on various topics, including researcher conflicts of interest. Both these programs and guidelines aid institutions in raising the quality of their human participants protections. OHRP has created a self-assessment tool for institutions to evaluate their human subjects protection programs and offers site visits to provide specific advice for the institution on how to improve their protection programs and to create a continuous quality improvement program. The self-assessment tool is still awaiting approval from the Office of Management and Budget (to comply with the Paperwork Reduction Act). It helps institutions assess the workload of their IRBs, the infrastructure and resources devoted to IRBs, the skills and training of their researchers and IRBs, etc.

OHRP draft guidelines on financial relationships in human participants research address financial conflicts of interest in five areas: the institution, clinical investigators, IRB members and staff, IRB review, and consent. If adopted, the guidelines will provide a uniform perspective on how one should approach these issues in order to promote ethical research and the protection of human participants. They respond to the fragmented nature of official regulations and the lack of general consensus about how one should evaluate and respond to these financial conflicts.

The QIP can certainly improve the quality of IRBs at institutions volunteering to undertake it. The voluntariness of the QIP means that any positive changes encouraged by the QIP will only occur at interested and committed institutions that devote resources to the self-assessment and quality improvement process, not across all institutions.

Most importantly, the "Common Rule" limits OHRP's initiatives and therefore it cannot address some of the key problems. OHRP cannot apply federal regulations to all research, especially to those institutions, such as reproductive facilities, not receiving federal funds. Further, its enforcement efforts may have the unintended consequence of mitigating efforts to streamline repetitive, time consuming reviews; institutions worried about more aggressive audits and compliance actions become hesitant to defer review. In addition, there has been little action to enhance the adverse event reporting system or collect systemic performance data.

Central IRBs: Individuals at NCI and OHRP have recently created a pilot central IRB (CIRB). This CIRB is currently focused on reviewing phase III trials of the cancer cooperative groups. The CIRB is an "expert IRB" that conducts initial and continuing review of protocols before distributing them to local IRBs or investigators. The local IRB would then have the option of conducting a time-efficient "facilitated review."

The structure of the CIRB program could eliminate some problems associated with the review of multi-site trials, such as the repetitive and time-consuming nature of the process. CIRB review could also reduce local IRBs' workloads, allowing them to direct precious resources elsewhere. The composition of the CIRB could also have important effects; each CIRB could include experts in the science of protocols reviewed, and no member would be employed by the home institution or the research sponsor other than NCI. This composition could increase the board's scientific expertise and mitigate inherent institutional conflicts of interest.

Importantly, realization of each of these positive changes depends on the local IRBs utilizing facilitated review. So far in the pilot program, local IRBs opted for facilitated review only fifteen times in a total of forty protocols. Furthermore, investigators are complaining that the CIRB has huge power and oversteps its authority by re-reviewing the scientific justification of research studies that have been thoroughly vetted scientifically, and that in this scientific review it lacks expertise. Having a central IRB review research studies does pose the problem of concentrated power, and mistakes that can be associated with such power. Other than recourse to local, institutional IRBs that understandably may be hesitant to approve a research study not approved by the CIRB, the current pilot program does not have a formal appeals process for adverse decisions made by the CIRB.

The CIRB program could also improve the review of adverse events by evaluating them "in the context of the entire clinical trial and on the basis of supplemental toxicity information provided by the NCI." This informed view is currently not possible on the local level.

Each of the proposed solutions discussed above would improve the protection of human research participants. However, most are specific in aim, responding to one or another specific problem. None of the currently proposed reforms is even meant to address the whole range of problems-the structural, process, or performance assessment problems-identified. Even taken all together, these reforms leave many problems partially or entirely unaddressed, largely because they take the current local, institution based IRB system as codified in the federal regulations as more or less fixed. The changes are relatively small changes around the edges of the extant system.

We propose a more systematic reform on the structural level, which would achieve the successes of these other reforms while also countering problems more comprehensively.

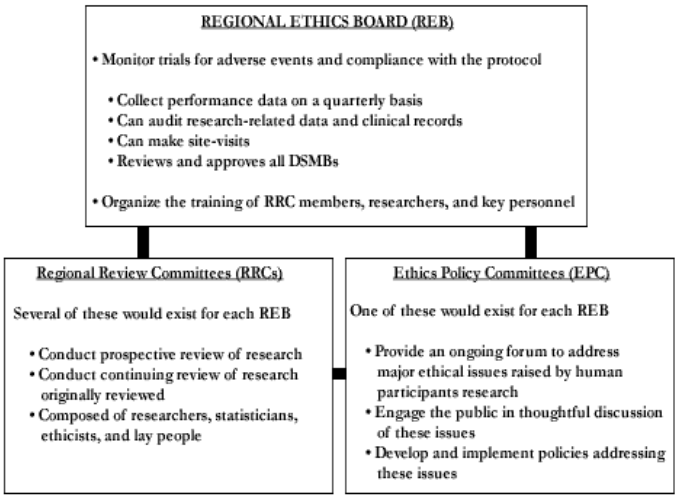
A MORE COMPREHENSIVE SOLUTION: REGIONAL ETHICS BOARDS

Comprehensively addressing the general structural, IRB process, and performance assessment problems affecting human research participants protection system requires fundamental change to the current system's structure. Two central changes seem necessary: 1) extend the federal regulations to all research; and 2) abandon institutional-based local review and consolidate all independent reviewing, monitoring, training, and ethical policy formulation into Regional Ethics Boards (REBs).

Extending the federal regulations to all human participants research is not an original idea. In addition to its inclusion in currently proposed legislation, NBAC endorsed it, and some bioethicists have been advocating this change for decades. The establishment of Regional Ethics Boards (REBs) in the place of local, institution-based IRBs would more dramatically affect the structure and process of research review. In our proposal, a REB would consolidate all activities related to human subjects protections for a given geographic region of the United States. Each REB would be a relatively large organization composed of several divisions. One division would include Research Review Committees-the actual panels that review research studies proposed by investigators. Another would be Ethics Policy Committees that propose ethical policies for the REB. Another would include liaisons between the REB and particular institutions and bodies conducting research in the geographic regions. At each major research institution, a single liaison would be dedicated to the institution; in other cases, one liaison may have

responsibility for working with a number of medical practices or smaller institutions that conduct less research. The liaisons would have a coordinating function that encompassed submission of the research studies, education of the members of the institutions and the like. Each REB would have four main responsibilities: 1) conducting prospective review of every research trial in their geographic area; 2) monitoring these trials for adverse events and compliance with the protocol; 3) organizing the training of clinical researchers and their teams; and 4) developing and refining policies regarding major ethical issues in human participants research. OHRP, or a similar federal oversight body, would coordinate, oversee, monitor, and compile data on all of the REBs.

OHRP: coordinates, oversees, monitors, and compiles data on REBs.



Prospective review: In order to manage the responsibility of reviewing all proposed research in one geographic area, each REB would establish multiple committees or panels to perform the actual reviews of research studies. These Research Review Committees (RRCs) should meet frequently, preferably weekly. Their members would include researchers, statisticians, ethicists, and lay people. At least 25% of the members should be lay people of various backgrounds. Each REB should establish standard operating procedures, to which all the RRCs of that REB would adhere. The REB would also have uniform policies and guidance for major issues in review, such as payment of participants, minimal risk procedures, confidentiality of data, and consent monitoring.

Each research study should be submitted to and reviewed by one, and only one, REB. For multi-site trials, approval by one REB would count as sufficient review for all participating sites, even sites outside the region of the REB. The REB conducting this review would be determined by the geographic region of the study's principal investigator. When a study has a foreign principal investigator, the review in the United States would occur in the region of the highest ranked American co-investigator.

If a REB rejects a research study, even after giving the investigators the opportunity to revise and resubmit, investigators should still be able to seek approval through a central appeal process. The federal oversight body would select another REB to review the research study. The ultimate judgment of that REB "appeal" would be final.

To monitor and enhance the performance of REBs, each should provide a quarterly performance report to the federal oversight body. This report would also be available to the public. It should include: 1) the number of research studies submitted, stratified by disease focus, whether participants were children, adults, or both, phase of study, sponsorship, number of sites participating, and number of multi-national sites; 2) the number of research studies exempted from review; 3) the number of research studies given expedited review; and 4) the average time from submission of a completed research study protocol to initial review, and time from revision or resubmission to final disposition.

The REB that originally reviewed and approved a research study would also conduct all continuing reviews and receiving and reviewing amendments to the study.

Monitoring: REBs should monitor the conduct of each research study that they review and approve. Monitoring would encompass at least three tasks. First, on a quarterly basis, each REB would collect the following performance data: 1) the number of people approached to enroll in the study, stratified by age, sex, and race; 2) the number of participants enrolled in each study; 3) the number of participants removed from the study and the reasons for the removals; 4) the number of participants who withdrew from the study; 5) the number of participants who experienced Grades III and IV toxicities and unexpected toxicities; and 6) the number of participants who died during the study and which deaths were research related. These data should be forwarded to the federal oversight body for collation and public dissemination. Second, REBs should have the power to audit all research-related data and clinical records. They should also have the authority to make site visits in order to ensure that research studies are implemented as specified in research protocols. Finally, REBs should have the responsibility of reviewing and approving the membership and schedule of all data safety and monitoring boards (DSMBs), and they should receive the determinations and reports from DSMBs after each DSMB meeting.

Training: Each REB should assume responsibility for training the RRC members and the investigators and key research personnel in its geographic region in the ethics of human participants research. Each REB should develop curricula and course programs, including basic, more advanced, and specific courses to ensure that all RRC members, investigators, and key personnel have appropriate training.

Developing Ethics Policies: In reviewing research studies, RRCs will confront major ethical issues, either specific to one

study or common to different types of studies. RRCs may also anticipate ethical issues that have not yet arisen in the context of a specific research study but are likely to arise in the future. To address these issues, each REB should establish a permanent Ethics Policy Committee (EPC), which should be administratively separate from the RRCs reviewing the individual research studies. In considering ethical issues, EPCs should be encouraged to think about the wider implications of the issue. For example, EPCs might become concerned with defining vulnerable populations and which protections should be afforded them, the policies regarding paying children to participate in research, and access to research drugs and interventions after the conclusion of the research study.

EPCs would make possible a more systematic and deliberative evaluation of major ethical issues. The practical goals of EPCs should be threefold: 1) To provide an ongoing forum to address major ethical issues raised by human participants research; 2) to engage the public in thoughtful discussions of these ethical issues; and 3) to develop and implement coherent and consistent policies addressing these issues for their associated REB. To fulfill these goals once aware of a major ethical issue, an EPC should first convene public deliberations on the issues, inviting experts as well as lay people to provide input. An EPC should then write an initial report on the topic. Such reports should serve as the foundation for a series of more focused public discussions that would provide the EPC with an opportunity for revision. Ultimately, the EPC should make a recommendation to the REB on actual policies for implementation. Through these policies should be developed for a specific REB, other REBs should be able to access them and consider whether they should adopt similar policies.

The composition of each EPC should be specified by that committee's REB. Generally speaking, though, EPCs should include researchers, experts in human participants research, bioethicists, and lay people. Equally or more important, perhaps, is the commitment of each member of the committee. Traditionally, National and Presidential Commissions are composed of members for whom service on the commission is not a primary responsibility. While this practice permits the participation of members who are both experienced and of national and international stature, it also means that members cannot devote their full attention to the Commission's work. However, including only full time employees on a commission or committee would preclude the participation of people with broader experience in research ethics and bioethics. Consequently, we suggest that members of each REB's EPC devote a specified portion of their time to the committee for a period of service.

Finally, the federal oversight board should ensure collaboration and coordination among REBs through regular meetings of all REBs. These meetings would have several objectives: 1) publicizing and sharing of performance data both about the REBs and about the clinical research they oversee; 2) sharing of "best practices" and standard operating procedures; 3) discussing EPC reports; and 4) collaborating on projects of shared interest, such as developing software for tracking research studies.

Addressing the problems of the current system: Does a proposed system of Regional Ethics Boards with the powers specified do a more comprehensive job of addressing the identified shortcomings of the current human protections system?

TABLE 3: How Well Regional Ethics Boards Address the Problems with the Human Research Participants Protection System

PROBLEMS	REGIONAL ETHICS BOARDS
1. Not all research covered by federal regulations	Yes
2. No mechanism for addressing major ethical issues	Yes
3. Exclusive reliance on local, institution-based review	Yes
4. Absence of resources devoted to IRBs	Yes
5. Lack of attention to inherent institutional conflcts of interest	Yes
6. Poorly defined IRB role in identifying and managing researchers' and IRB members' conflicts of interest	No
7. Inadequate education of clinical investigators and IRB members	Yes
8. Repetitive review process	Yes
9. Time-consuming review process	Partially
10. Poor quality control of IRB reviews	Yes
11. Excessive focus on informed consent forms	Partially
12. Deficiencies in monitoring and continuing review	Yes
13. Inefficient and ineffective adverse event reporting	Yes
14. Insufficient evaluation of IRB effectiveness	Yes
15. No systematic collection and dissemination of perfrmance data	Yes

OBJECTIONS CONSIDERED

If creating a system of REBs would address most of the problems outlined, prudence requires inquiry about what problems this reform might exacerbate or create. First, many investigators and others view the process of research review and the regulations as a hurdle to overcome, rather than as important and integral to their work. Removing the review process from

researchers' home institutions might only increase the sense of separation that investigators and others feel toward review board members and the regulations that they abide by.

Several components of the REB system act to avoid this possibility. First, the REB system would counter many of the underlying causes of this sentiment. The clarification of policies through standard operating procedures, decrease in time required by the review process, and elimination of the repetitiveness of the process should mitigate some of the reasons investigators feel frustrated with the current system.

More importantly, however, are the positive actions undertaken by REBs to promote sincere commitment among investigators and institutions to the ethical conduct of research. Much of the current educational material offered to investigators and personnel focuses on becoming familiar with applicable regulations. Many of the curricular materials are not well developed because of lack of time and resources. REBs should have resources to devote to developing better training materials and programs. Second, concentration of review in REBs creates a concentration of power. Each REB will wield considerable authority over the design, conduct, and monitoring of research studies. This could become a Kafkaesque situation leaving investigators feeling that they are at the mercy of one central power over which they have very little influence and with little authority to dictate the content of their own research studies. Creation of a formal appeals process and performance measures for the REBs are attempts to diffuse the possible negative consequences of this concentration of power. The appeals process provides researchers with an opportunity to ask for an evaluation from another REB, and it should be helpful if the disagreement is about different but equally ethical approaches to particular issues.

Third, the uniformity of the REB system could lead to rigidity within the system. One of the advantages of the current IRB system is that the multitude of IRBs reviewing studies encourages the adoption of varied ethical approaches to single issues. Unfortunately in the current system, varied approaches have become more akin to unjustified inconsistencies than thoughtful variation. The issue is whether coordinated regional boards can avoid rigidity. By proposing the creation of diverse REBs-rather than one central IRB-with formal evaluation of procedures and performance data of the IRB, we hope for the promotion of healthy competition and a reduction in rigidity.

Fourth, local, institution based IRBs bring knowledge of the local circumstances, especially the integrity and care of individual investigators, the institutional infrastructure for protecting participants, and concerns of the community. This local knowledge would be lost by regional REBs.

Local knowledge is a double edged sword. It is the case that knowledge of imprudent investigators-so called "cowboys"-and lax oversight can assist IRBs in carefully reviewing specific research protocols. However, it can also lead to the problems of institutional conflicts of interest identified previously, where the protocols of influential or well-liked researchers may not be as carefully scrutinized by local IRBs. Furthermore, the value of local knowledge for the review of research protocols has never been demonstrated to improve protections. Finally, the proposal for REBs includes having local liaisons that can provide the knowledge of local circumstances. Currently the for-profit IRBs are able to obtain local knowledge through such liaisons.

Finally, the cost of implementing a new system of REBs could be very high. No one knows the actual costs of the current human protections system. But we can obtain an estimate of the cost. Currently, it is estimated that there are 4 to 6,000 IRBs. Some of the biggest institutions spend millions supporting their human research protections infrastructure. For instance, it was recently state that Johns Hopkins increased it spending on its IRBs from $1 million to $2 million per year. Some of the larger for-profit IRBs may spend even more. Smaller institutions probably spend considerably less. If the average is a very modest $50,000 per institution per year-about the cost of a single support staff person, office space, and copying-then the total cost for the current human research protections system is between $200 and $300 million per year. A crude estimate of the cost of the REBs for performing all the functions delineated would be approximately $20 million per year. Assuming 10 REBs for the entire country would mean the cost of the system would be $200 million per year, comparable to the cost of the current system. Though a large sum, this amount seems a comparatively small amount of money to ensure the ethical nature of research with human participants that costs more than $40 billion dollars per year in the United States.

CONCLUSION

The current system of protecting human research participants is firmly rooted in review and oversight at on the local, institutional level. The rationale of reason and convenience that originally led to this structure, however, no longer holds for the modern research endeavor. Not only does the research community and public feel that it has become burdensome and inefficient, but it has contributed to participant harms.

While many groups are attempting to respond to these issues, they do so in a piecemeal fashion that addresses only specific issues. We propose a more comprehensive solution - a system of REBs, RRCs, and EPCs - that completely restructures the system of human participants protections. In doing so, this new system promotes protection of human participants in research while alleviating the distress of the research community, honoring both the interests of human participants and the interests of the research community.

ENDNOTES

1. By "health research," we mean clinical research, epidemiological research, and social science research relevant to human health issues.